DOCKING STUDIES ON THE INHIBITION OF CHOLINE KINASE

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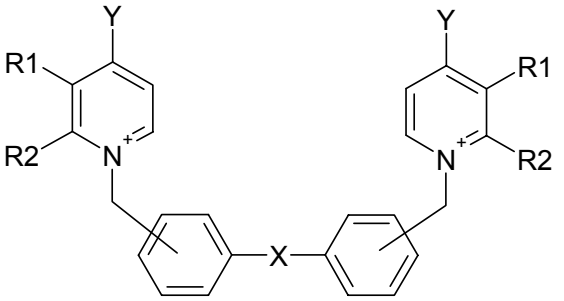
Our research group has described several human choline kinase (ChoK) inhibitors that show antiproliferative activity [1]. Recently, a crystal structure of *C. elegans* Choline Kinase (CKA2) has been resolved and important residues for the catalytic activity has been identified by site-directed mutagenesis [2,3].

In this communication, we present our findings on a possible mechanism for the inhibition of choline kinase by a series of bispyridinium and bisquinoliniun compounds of general formula **1.**



1

X= CH_2, $(CH_2)_2$, CH=CH
Y= NH_2, NR_2, etc
R_1=R_2= H, -$(CH)_4$-

A homology model of ChoK has been constructed based on the crystal structure of CKA2, and putative binding-sites for both choline and ATP have been identified according to the known site-directed mutagenesis data.

Docking studies reveal that most of these inhibitors occupy simultaneously both choline and ATP binding-sites. A qualitative structure-activity relationship between docking geometries and inhibition activity has been found, that supports our ChoK model.

[1] Conejo-Garcia, A.; Campos, J. M.; Sanchez-Martin, R. M.; Gallo, M. A.; Espinosa, A. Bispyridinium Cyclophanes: Novel Templates for Human Choline Kinase Inhibitors. *J. Med. Chem.* **2003**; 46(17); 3754-3757.
[2] Daniel Peisach, Patricia Gee, Claudia Kent and Zhaohui Xu. The Crystal Structure of Choline Kinase Reveals a Eukaryotic Protein Kinase Fold. *Structure*, **2003**, *11*, 703–713.
[3] Chong Yuan and Claudia Kent. Identification of critical residues of choline kinase A2 from Caenorhabditis elegans. *J. Biol. Chem*., **2004**,. *279 (17),* 17801-17809.